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(54) Title: 5-HALO-TRYPTAMINE DERIVATIVES USED AS LIGANDS OF THE 5-HT₆ AND/OR 5-HT₇ SEROTONIN RE-
CEPTORS

(57) Abstract: Compounds of Formula (I): (I); wherein: R₁ and R₂ either the same or different, are H or linear or branched C₁-C₆ alkyl; R₃ = linear or branched C₁-C₆ alkyl; R₄ = halogen, and pharmaceutically acceptable salts thereof are useful as active ingredients in the preparation of medicaments used as ligands of the 5-HT₆ and/or 5-HT₇ serotonergic receptors.

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5-halo-tryptamine derivatives used as ligands of the 5-HT₆ and/or 5-HT₇ serotonin receptors

The invention described herein relates to 5-halogenated tryptamine derivatives useful as ligands of the 5-HT₆ and/or 5-HT₇ serotonin receptors, processes for their preparation, their use as medicaments, in particular for the treatment of nervous system pathologies associated with serotonin level deficit, systemic pathologies involving the cardiovascular system, the gastrointestinal tract and the pharmaceutical compositions comprising them.

Background of the invention

Over the past 10 years, molecular cloning has revealed 14 serotonin subtypes that have been divided into 7 subfamilies. The large multiplicity of serotonin receptors has been suggested to be a direct result of the evolutionary age of 5-HT system. With the exception of 5-HT₃ receptors which are ligand-gated ion channels, all of receptors are members of the serotonin receptor superfamily belonging to a large class of receptors linked to their effector functions via G-protein. (Gerhardt, C.C. et al., *Brain Res.* 746:207-219, 1997; Hoyer, D. et al., *Neuropharmacol.* 36:419-428, 1997).

In 1994, 5-HT₆ serotonin receptors were discovered on pig nucleus caudatum and cerebellum membranes. Since then, 5-HT₆ serotonin receptors have been observed in the olfactory tubercle, frontal and entorinal cortex, nucleus accumbens, striatum, hippocampus and in the molecular layer of the cerebellum. 5-HT₆ serotonin receptors appear to be almost exclusively present in the brain and in 5-HT projection fields and not in the 5-HT neurons of raphe nuclei suggesting that 5-HT₆ receptors probably have a postsynaptic role. It has been further discovered that

5-HT₆ receptors are members of the G-protein superfamily and they are positively coupled to an adenylate cyclase second messenger system.

Serotonin binding to the 5-HT₆ receptors induces an activation of the adenylate cyclase enzyme, with concomitant increase of intracellular cAMP levels. The recent discovery of 5-HT₆ serotonin receptors has stimulated research into 5-HT₆-selective ligands to demonstrate uniqueness of the new receptor subfamily and its own exact clinical significance. It is actually known that many psychoactive drugs (antidepressants, antipsychotics) exhibit high affinity for 5-HT₆, however, without selectivity (Monsma, F.J. et al., *Molecular Pharmacology* 43:320-327, 1993; Roth, B.L. et al., *J. Pharmacol. Exp. Ther.* 268, 1403-1410; 1994) and that 5-HT₆ receptors might modulate cholinergic neurotransmission in the central nervous system. Furthermore, 5-HT₆ receptors displayed on GABA-containing neurons in the striatum and on glutamate-containing neurons of hippocampus have been suggested to mediate endogenous serotonin actions. Thus, ligands for 5-HT₆ receptors might be useful to treat: motor disorders, depression, anxiety, mood disorders, memory disorders, Huntington's disease, Parkinson's disease and Alzheimer's disease. (Branchek, T.A. and Blackburn, T.P., *Annu. Rev. Pharm.Toxicol.* 40: 319-34, 2000).

5-HT₇ serotonin receptors were identified in several rodent and human tissues. In rat brain, 5-HT₇ receptors appear with particularly high distribution in hypothalamus, thalamus and hippocampus, while lower 5-HT₇ receptor RNAm levels were found in the cerebral cortex, striatum, olfactory bulb and olfactory tubercle. The presence of 5-HT₇ receptor RNAm is not limited to the brain, it has also been found in peripheral tissues (spleen, stomach, intestine, heart, coronary artery). 5-HT₇ receptors are functionally coupled to adenylate cyclase enzymatic system. Pharmacological *in vitro* evidences demonstrate increase of endocellular cAMP levels following 5-HT₇ receptor stimulation. As with 5-HT₆ se-

rotonin receptors, the clinical value of 5-HT₇ receptors is not currently known (Sleight, A.J., Boess, F.G., Bourson, A., Sibley, D.R., Monsma, F.J., 1997 *DN&P* 10 (4):214-224). It has been suggested that 5-HT₇ receptors might be involved in the mechanisms regulating blood pressure. 5-HT₇ receptors' high distribution on the blood vessels and pharmacological data demonstrating vasodilatation following serotonin binding to the 5-HT₇ receptors suggest utilization of 5-HT₇ ligands as hypotensive agents (Martin, G.R. and Wilson, R., (1995) *British J. Pharmacol.* 114: 383P). Furthermore, it was previously demonstrated that 5-HT₇ receptors, abundantly present in the hypothalamus, are implicated in the control of circadian rhythm of spontaneous neuronal electrical activity in the central nervous system (Lowenberg, T.N. et al., *Neuron* (1993) 11:449-58).

Thus, 5-HT₇ ligands may be modulator agents of many processes regulated by circadian rhythm particularly sleep cycle whose desynchronization induces sleep disorders. Other evidences demonstrate that 5-HT₇ receptors might be involved in the pathogenesis and treatment of depression. The observation that, 5-HT₇ receptor binding sites in rat hypothalamus determine a down-regulation following chronic treatment with antidepressant Fluoxetine, has supported this therapeutic indication (Sleight, A.J. et al., *Mol. Pharm.* (1996), 47: 99-103). The strict classical notions of neurotransmitter dysregulation hypothesis that associate depression with a deficiency of available neurotransmitter or subsensitivity of mainly noradrenergic and/or serotonergic receptor systems have recently been expanded to include disturbances in biological rhythm regulation. Impairment of the efficiency of rhythm maintenance or rhythm desynchronization has been suggested by many to lead to mental fatigue and depression (Goodwin F.K., Wirz-Justice A., Wehr T.A., 1982. In Costa Ragni (eds.), *Typical and atypical antidepressant: Clinical practical*).

Although melatonin is generally thought to be a primary modulator of circadian functions, serotonin also plays a critical role, particularly acting on 5-HT_{1a}, 5-HT_{1b}, 5-HT_{2a}, 5-HT₇ subtypes in the suprachiasmatic nucleus of the hypothalamus (Van Den Pol, A.N., Dudek, F.E., (1993) *Neuroscience* 56:793-811; Mullins, U.L., et al., (1999): *Neuropsychopharmacology* 21, (3) 352-367).

Contemporary localization of 5-HT₆ and 5-HT₇ receptor sites, although with different density of distribution, in brain areas (hippocampus, frontal cortex) implicated functionally in the attention and learning processes and that same ability on the part of both receptors to increase endocellular cAMP levels following their stimulation have suggested that agents binding both 5-HT₆ and 5-HT₇ receptor might modulate neuronal plasticity mechanism underlying the acquisition and subsequently the learning processes of an individual.

Ligands with contemporary affinity for 5-HT₆ and 5-HT₇ receptors might have a therapeutic use in conditions requiring an improvement in cognitive processes (Menese, A., (1999) *Neurosci. Biobehav. Rev.*, 23 (8):1111-25).

Probable use of 5-HT₇-ligands in treatment of irritable bowel disease has been suggested by recent evidence. Gastric hypomotility is thought to be one of the mechanisms underlying pathophysiological mechanism of this syndrome and remains an attractive therapeutic target. Actually a new generation of prokinetics includes 5-HT₄ receptor ligands (tegaserod, prucalopride). Preliminary evidence arouses interest in research of 5-HT₇ receptor ligands to be directed toward the above therapeutic target (De Ponti, F., Tonini, M., (2001) *Drugs*, 61 (3):317-332). In fact, the observation that 5-HT₇ receptors mediate smooth muscle relaxation and 5-HT₇ binding sites localization on intestine tissue should suggest therapeutic use of 5-HT₇ receptor ligands.

At the present, compounds with affinity for the 5-HT₆ receptor have been identified belonging to different chemical classes. For example, EP 0 815 861 and EP 0 930 302, Hoffmann-La Roche, describe sulphonamides and benzosulphonate derivatives as selective ligands for the above-mentioned receptors; WO 98/27058, SmithKline Beecham, describe carboxamide indole derivatives as 5-HT₆ receptor antagonists, whilst WO 98/27081 and WO 99/42465, SmithKline Beecham, describe, amongst others, sulphonamide derivatives, as does US 6,187,805, Merck Sharp and Dohme; WO 00/12623, SmithKline Beecham, describes sulphonate and sulphonamidederivatives; WO 00/37452, Merck Patent, describes sulphonyloxazolylamines; WO 00/63203 and US 6,133,287, Allelix Biopharmaceutical Inc., describe piperidinoindoles as acting as 5-HT₆ antagonists.

Tryptamine derivatives are well-known for several pharmacological uses. WO 97/06140 describes their use for the treatment of pathologies correlated with melatonin disturbances; WO 97/46525 and WO 98/23587 as selective ligands of the 5-HT_{1D} receptor and their use in the treatment of migraine; WO 97/48680 for the treatment of vasospasms; WO 98/06695 for dermatological treatments; WO 98/47868 as combined activity antagonists of various subtypes of the 5-HT₁ receptor; WO 00/11619 as selective antagonists of the 5-HT_{2A} receptor; WO 99/51576 for the treatment of nervous disorders associated with the serotonergic system; WO 99/54301 as antibacteric agents; WO 00/37441 for the treatment of cardiovascular, ischaemic, parasitic, inflammatory, neurodegenerative diseases, myopathy and sickle-cell anemia; WO 00/78716 and WO 00/44721 as active agents on the adrenergic system.

Other tryptamine derivatives are noted for their activity against serotonergic receptors different from 5-HT₆, for example WO 95/14004, WO 95/24200, WO 96/26922, WO 96/26923, WO 97/13512, WO 99/51576, EP 1023898 and WO 00/52002.

Regarding compounds with specific activity against the 5-HT₆ receptor, WO 99/47516, Slassi et. al. describes 1-acyl or 1-sulphonylindole substituted at position 3 with an alkylpyrrolidine with affinity for the 5-HT₆ receptor. WO 99/65906, Allelix Biopharmaceuticals Inc. discloses bicyclic piperidines and piperazines linked to an indole residue as inhibitors of the 5-HT₆ receptor.

Patent application WO 00/34242, Virginia Commonwealth University, discloses serotonin derivatives with increased affinity and selectivity for the 5-HT₆ receptor. Patent application WO 00/63203, Allelix Biopharmaceuticals Inc., discloses 1-acyl or 1-sulphonylindoles, substituted at position 3 with a piperidine, having affinity for the 5-HT₆ receptor.

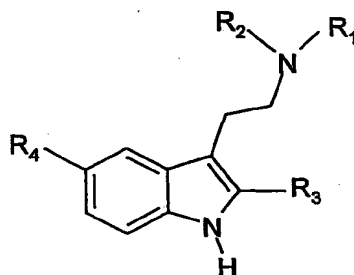
As for the 5-HT₇ receptor, WO 00/37082, SmithKline Beecham, discloses the use of 5-HT₇ receptor antagonists described in WO 97/29097, WO 98/48681 and WO 97/49695 for the treatment of neuronal degenerations resulting from ischemic events; EP 0 998 923, BASF, discloses the use of 5-HT₇ receptor antagonists in the prevention of ischemias, in particular infarction; WO 99/54303 and WO 98/00400, Meiji, discloses tetrahydrobenzindoles for the treatment of mental and circulatory disorders.

Abstract of the invention

The present invention relates to tryptamine based ligands with affinity for the 5-HT₆ and/or 5-HT₇ serotonin receptors. From a therapeutic point of view, these agents can be used for the treatment of nervous system pathologies, associated with serotonin level deficit, systemic pathologies involving the cardiocirculatory system (hypertension) and gastrointestinal tract (irritable bowel disease).

It is known that many disorders of the central nervous system are effectively treated by the use of drugs which can interact specifically with serotonin receptors, and for this reason, clinically approved for the treatment of migraine, depression, hypertension, psychosis and mental fatigue, sleep disorders and other effects derived from the desynchronisation of circadian rhythms.

It has now been found that compounds of Formula (I)



(I)

wherein:

R₁ and R₂, the same or different, are H or C₁-C₆ linear or branched alkyl;

R₃ = C₁-C₆ linear or branched alkyl;

R₄ = halogen;

have affinity for the 5-HT₆ and/or 5-HT₇ receptors.

Accordingly, it is an object of the present invention the use of compounds of Formula (I) above and the pharmaceutically acceptable salts thereof for the preparation of medicaments useful as ligands of the 5-HT₆ and/or 5-HT₇ serotonergic receptor, in particular for the treatment of nervous system pathologies associated with serotonin level deficit, systemic pathologies involving the cardiocirculatory system, in particular hypertension; the gastrointestinal tract, in particular irritable bowel disease.

Other objects of the present invention are new compounds of Formula (I) from which are excluded compounds where R₄ is fluoro, chloro or bromo,

R₃ is methyl or ethyl, R₁ and R₂, the same or different, are hydrogen and methyl; a process for the preparation of said new compounds of Formula (I), their use as medicaments, in particular for the treatment of nervous system pathologies associated with serotonin level deficit, systemic pathologies involving the cardiovascular system, in particular hypertension; the gastrointestinal tract, in particular irritable bowel disease and pharmaceutical compositions containing said compounds as active ingredients.

Detailed description of the invention

In the compounds of Formula (I), the terms C₁-C₆ alkyl are intended to mean the methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, tert-butyl, pentyl, hexyl, and all the possible isomers, preferably methyl and ethyl.

For halogens, the meaning is fluoro, chloro, bromo and iodio, preferably chloro and bromo.

Among the Formula (I) compounds, a first preferred group comprises those compounds in which the groups R₁ and R₂ are the same, particularly methyl.

A second preferred group comprises Formula (I) compounds wherein R₃ is alkyl, as defined above, in particular methyl or ethyl, and R₄ is chloro. Formula (I) compounds wherein R₄ is chloro have selective affinity for 5-HT₆ serotonin receptor, therefore are useful for the preparation of medicaments useful as ligands of the 5-HT₆, for example for the treatment of depression, mood disorders, psychosis, schizophrenia, motor disorders, cognitive disorders, Parkinson's disease, Alzheimer's disease, Huntington's disease.

A third preferred group comprises Formula (I) compounds wherein R_3 is alkyl, as defined above, in particular methyl, and R_4 is bromo.

Particularly, when R_4 is bromo the molecule also acquires affinity for the 5-HT₇ receptor subtype.

By virtue of this property, the compounds are indicated in the treatment of depression, migraine, hypertension, in particular for the improvement of the individual learning process, to counteract the desynchronisation of the biological rhythms and the many alterations derived therefrom (mental fatigue, depression, sleep disorders).

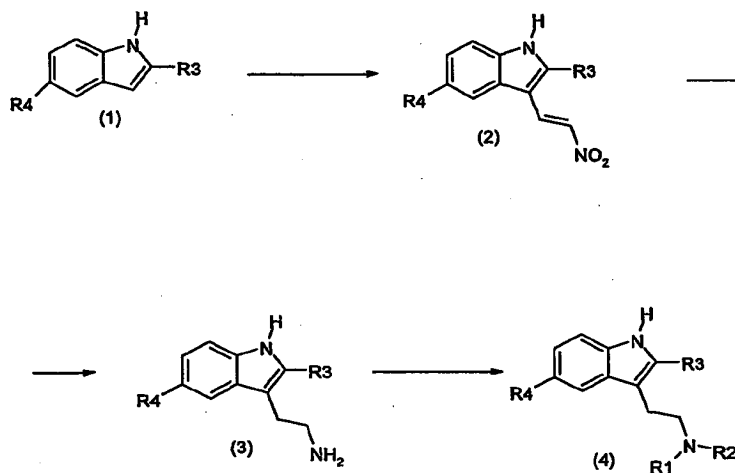
Particularly preferred are the compounds 5-bromo-2-methyl-N,N-dimethyltryptamine (ST 1938), 5-chloro-2-ethyl-N,N-dimethyltryptamine (ST 2253) and 5-chloro-2-methyl-N,N-dimethyltryptamine (ST 1936).

Formula (I) compounds wherein R_3 is methyl, R_1 and R_2 are the same or different and are hydrogen and methyl are described in Chapman, N.B. et. al., *J. Chem. Soc.* 1965; 1424-1428.

The compounds according to the present invention, can be prepared by the process illustrated in the following scheme according to procedures reported in the literature for analogous compounds (Spadoni, G. et. al., *J. Med. Chem.*, 1993;36 (25): 4069-74).

Those of ordinary skill in the art will be able to choose the correct starting compounds and the corresponding reagents and reaction conditions in relation to the desired final product relating to the above mentioned Formula (I).

The process according to the present invention is carried out according to the scheme 1 reported below.



The starting compound, 5-halo-2-alkyl-indole is commercially available or can be prepared by analogy as described in *J. Med. Chem.* 1993, 36, 4069, but see also *JOC* 1994, 59, 6372-6377.

The Formula (1) compound is reacted with 1-dimethylamino-2-nitroethylene, which is commercially available. The molar ratios are not critical, as an example it is convenient to react the compounds in equimolar amounts, even if an excess of one or the other could be envisaged in relation to the different Formula (I) final products. The reaction is carried out in trifluoroacetic acid, at a temperature and for a time that can be chosen in relation to the reagents, their concentrations and the solvents used. Suitably, the reaction can proceed at low temperatures, for example 0°C, up to a temperature compatible with the reaction conditions and the absence or reduced quantities of secondary products or of degradation, and for times from a few minutes to several hours.

Compound (2), if desired, is isolated from the reaction medium using conventional techniques known by those skilled in the art, it is then subjected to reduction of the ethyl double bond adjacent to the nitro group, to give the corresponding saturated derivative (3). For the considerations relating to the reaction conditions, those skilled in the art could gain these from the preceding paragraph.

The final step gives the functionalisation of the primary amino group with the groups given in the definitions for R_1 and R_3 . This is done by conventional methods noted in the literature, for example *J. Org. Chem.* 37, 1673-1674 (1972).

The following examples further illustrate the invention.

EXAMPLE 1

(E)-5-Bromo-2-methyl-3-(2-nitroethenyl)-1H-indole

To a solution of 0.58 g of 1-(dimethylamine)-2-nitroethylene (5 mmol) in 5 mL of trifluoroacetic acid, stirred and cooled to 0°C, 1.05 g (5 mmol) of 5-bromo-2-methyl-indole is added and the resulting mixture is left to react at room temperature, under nitrogen, for 30 minutes. The reaction mixture is then placed into an ice-water bath. The aqueous solution is extracted with ethyl acetate and the organic phases combined, then washed with a saturated bicarbonate solution, and then water and finally dried over anhydrous sodium sulphate. After filtration, the solvent is removed at low pressure, leaving a solid, orange-coloured residue, which is then suspended in an ethyl acetate - ether mixture and filtered.

Yield: 89%

R_f = 0.3 (cyclohexane/EtOAc :1)

M.p.: 196 - 198°C (dec.)

^1H -NMR (200 MHz)(DMSO- d_6): δ 2.59 (s, 3H), 7.34 (m, 2H), 7.97 (d, 1H, $J = 13.2$ Hz), 8.06 (m, 1H), 8.26 (d, 1H, $J = 13.2$ Hz)
EIMS: m/z 280, 282 (M^+), 154 (100)

5-bromo-2-methyltryptamine hydrochloride

A solution of nitroethenylindole (2) (1.7 g, 6 mmol), in 25 mL of anhydrous THF, is added dropwise to a suspension, under nitrogen at 0°C, of LiAlH_4 (1.2 g, 36 mmol) in THF (6.5 mL) and the resulting mixture is stirred for 5 hours at room temperature. After cooling to 0°C, the excess LiAlH_4 is destroyed by the careful addition of water and the resulting suspension filtered through celite. The solvent is evaporated under vacuum, the residue acidified with 2N HCl and then partitioned with water and ethyl acetate. The aqueous phase is then alkalized with 6N NaOH and extracted 3 times with ethyl acetate. The combined organic phases are washed with brine, dried over anhydrous sodium sulphate and concentrated under vacuum. The resulting free amine is then transformed into the hydrochloride salt by the addition of a solution of HCl in anhydrous methanol. The salt is then purified by crystallization in ethyl acetate.

Yield: 69%.

^1H NMR (200 MHz, (DMSO- d_6): δ 2,33 (s, 3H), 7.09 (dd, 1H, $J = 1,9$ and $J = 8,3$ Hz), 7.21 (d, 1H, $J = 8,3$ Hz), 7.65 (d, 1H, $J = 1,5$ Hz), 7.94 (br, s, 3H), 11,15 (s, 1H), 7.94 (br, s, 3H), 11.15 (s, 1H).

5-bromo-2-methyl-N,N-dimethyltryptamine (ST 1938)

A 40% solution of HCHO (0.95 mL) in 16 mL of MeOH, is added dropwise to a stirred solution of 5-bromo-2-methyltryptamine (0.8 g, 3.16 mmol), AcOH (0.47 mL) and NaCNBH_4 (0.35 g). This is let to react for 2.5 hours at room temperature under stirring; 5 mL of an aqueous saturated solution of K_2CO_3 is then added; methanol is evaporated under vacuum and the aqueous phase extracted with ethyl acetate.

The organic phases are dried over anhydrous sodium sulphate, and after evaporation of the solvent under vacuum an orange coloured oil is obtained, which is purified by filtration through silica gel and subsequent crystallisation from dichloromethane-hexane.

Yield: 56%

M.p.: 135-136°C

Rf = 0,52 (CH₂Cl₂/MeOH/TEA 9:0,4:0,4)

¹H NMR (200 MHz, (CDCl₃): δ 2,35 (s, 6H), 2,37 (s, 3H), 2,44-2,52 (m, 2H), 2,78-2,86 (m, 2H), 7,11 (d, 1H, *J* = 8,5 Hz), 7,18 (dd, 1H, *J* = 1,6 e *J* = 8,5 Hz), 7,60 (d, 1H, *J* = 1,6 Hz), 7,95 (br s, 1H).

EIMS: m/z 280, 282 (M⁺), 222, 224 (100).

EXAMPLE 2

Following the method described and in accordance with the scheme and example above, the following compounds were prepared:

(E)-5-chloro-2-methyl-3-(2-nitroethenyl)-1H-indole

Orange solid

Yield: 85%;

M.p.: 191-193 °C

¹H NMR (200 MHz, (acetone-d₆): δ 2,68 (s, 3H), 7,21 (dd, 1H, *J* = 1,95 and *J* = 8,5 Hz), 7,5 (d, 1H, *J* = 8,5 Hz), 7,85 (d, 1H, *J* = 13,3 Hz), 7,86 (d, 1H, *J* = 1,95 Hz), 8,30 (d, 1H, *J* = 13,3 Hz); EIMS: m/z 236 (M⁺), 154 (100).

5-chloro-2-methyltryptamine hydrochloride

Beige solid crystalline precipitated from EtOH/Et₂O.

Yield: 72%

¹H NMR (200 MHz, (DMSO-d₆): δ 2,33 (s, 3H), 6,97 (dd, 1H, *J* = 1,9 and *J* = 8,3 Hz), 7,25 (d, 1H, *J* = 8,3 Hz), 7,52 (d, 1H, *J* = 1,5 Hz), 8,03 (br, s, 3H), 11,15 (s, 1H).

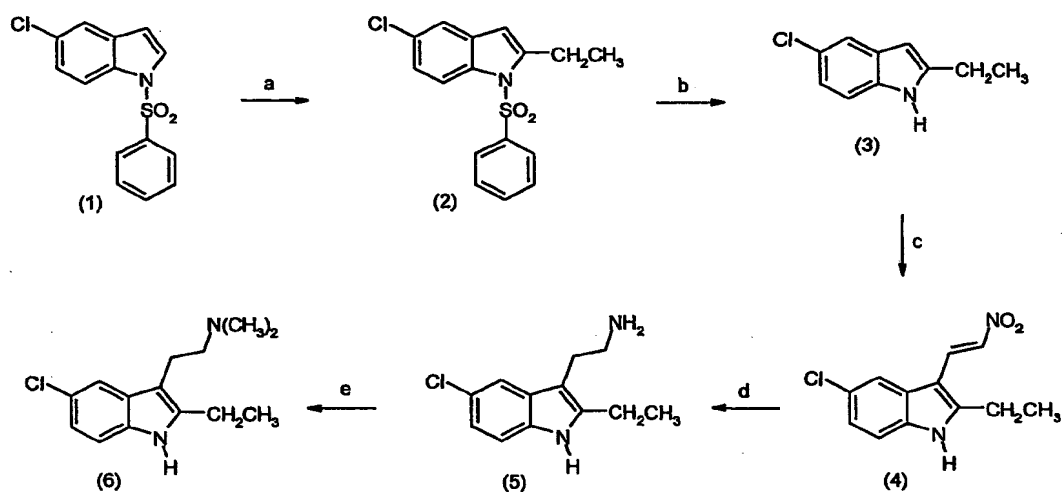
5-chloro-2-methyl-*N,N*-dimethyltryptamine (ST 1936)

White solid;

Yield: 75%;

M.p. = 126-127°C

^1H NMR (200 MHz, CDCl_3): δ 2,35 (s, 6H), 2,38 (s, 3H), 2,44-2,52 (m, 2H), 2,79-2,87 (m, 2H), 7,05 (d, 1H, $J = 1,9$ and $J = 8,6$ Hz), 7,17 (d, 1H, $J = 8,2$ Hz), 7,45 (d, 1H, $J = 1,9$ Hz), 7,86 (br s, 1H)

EIMS: m/z 236 (M^+), 178 (100).**EXAMPLE 3**

Reagents: (a) *t*-BuLi, THF, -20° C; EtI, -78° to room temperature, 2h; (b) 2N NaOH, MeOH, reflux, 40 h; (c) 1-(dimethylamino)-2-nitroethylene, TFA, 0°C, 0,5 h; (d) LiAlH_4 , THF, room temperature, 6h; (e) NaCNBH_3 , 40%, HCHO, MeOH, AcOH, room temperature, 2,5h.

***N*-(Benzensulfonyl)-5-chloro-2-ethylindole (2).**

t-BuLi (3.7 mL of 1.7 M solution in pentane) was added dropwise to a solution of *N*-(benzensulfonyl)-5-chloroindole (1) (*J. Org. Chem.* 1981, 46,

3859) (1.5 g, 5.14 mmol) in THF (35 mL) at -70°C , under a nitrogen atmosphere. The mixture was stirred for 15 min, allowed to warm to room temperature over 20 min, cooled to -70°C , and treated with a solution of ethyl iodide (0.84 mL, 10.5 mmol) in dry THF (5 mL). The mixture was stirred at -78°C for 1 h, allowed to warm to room temperature, stirred for 2h, poured into ice (15 g), and a saturated aqueous NH_4Cl solution and then extracted with ether (3 x 20 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated *in vacuo* to give a residue which was purified by flash chromatography (silica gel, cyclohexane/ethyl acetate, 8:2) and crystallization from ethylacetate/cyclohexane.

Yield: 80%

M.p.: 108°C (dec.)

^1H -NMR (MHz, CDCl_3): δ 1.33 (t, 3H), 3.01 (q, 2H), 6.35 (s, 1H), 7.23 (dd, 1H), 7.39-7.74 (m, 6H), 8.11 (d, 1H)

EIMS: m/z 319 (M^+); 178, 143 (100%)

5-Chloro-2-ethylindole (3)

A mixture of 2 (1.3 g, 4.07 mmol), 2N NaOH (12 mL), and MeOH (62 mL) was refluxed for 40 h. The organic solvent was evaporated and the remaining residue was extracted with EtOAc. The combined extract were washed with brine, dried (Na_2SO_4) and evaporated *in vacuo* to give a residue which was purified by flash chromatography (silica gel, cyclohexane/ethyl acetate, 8:2) and crystallization from ether/cyclohexane.

M.p. = 89°C

Yield 90%

^1H NMR (CDCl_3) δ 1.35 (t, 3H), 2.79 (q, 2H), 6.19 (s, 1H), 7.06 (dd, 1H), 7.21 (d, 1H), 7.49 (s, 1H), 7.92 (br s, 1H)

EIMS: m/z 179 (M^+); 164 (100)

(E)-5-Chloro-2-ethyl-3-(2-nitroethenyl)-1H-indole (4)

The indole **3** (5 mmol) was added to a stirred ice-cooled solution of 1-(dimethylamino)-2-nitroethylene (0.58 g, 5 mmol) in trifluoroacetic acid (5 mL). The mixture was stirred at room temperature under N₂ for 0.5 h and then poured onto ice water. The aqueous solution was extracted with ethyl acetate, the combined organic layers were washed with a saturated NaHCO₃ solution and then with water. After drying over Na₂SO₄, the solvent was evaporated under reduced pressure to give a crude orange solid which was suspended in a mixture of EtOAc-Et₂O and filtered, or chromatographed on silica gel (cyclohexane/EtOAc, 1:1, as eluent).

Yield: 89%

M.p.: 188°C dec.

¹H(CDCl₃) δ 1,42 (t, 3H), 3,02 (q, 2H), 7,21-7,34 (m, 2H), 7,68 (m, 1H), 7,72 (d, 1H), 8,3 (d, 1H), 8,68 (br s, 1H)

EIMS: m/z 250(M⁺), 203, 188 (100)

5-Chloro-2-ethyltryptamine (**5**)

A solution of the nitroethenylindole **4** (6 mmol) in dry THF (25 mL) was added portionwise to a stirred ice-cooled suspension of LiAlH₄ (1.2 g, 36 mmol) in dry THF (65 mL) under nitrogen and the mixture was stirred at room temperature for 5 h. After cooling to 0°C, the unreacted LiAlH₄ was destroyed by careful addition of water. The resulting mixture was filtered through a Celite® pad; the filtrate was concentrated *in vacuo*, then acidified with 2N HCl and partitioned between water and ethyl acetate. The aqueous phase was made alkaline with 6N NaOH and then extracted (3x) with EtOAc; the combined organic layers were washed with brine, dried (Na₂SO₄), and concentrated under reduced pressure to give a crude oily amine.

(oil); EIMS: m/z 222 (M⁺); 192 (100), 177

5-Chloro-2-ethyl-N,N-dimethyltryptamine (**6**) (ST 2253)

40% HCHO (0.95 mL) in MeOH (16 mL) was added dropwise to a stirred cooled (0°C) solution of (5) (3.16 mmol), AcOH (0.47 mL) and sodium cyanoborohydride (0.35 g). The resulting mixture was allowed to stir at 25 °C for 2.5 h. A saturated aqueous solution of K₂CO₃ (5 mL) was added, MeOH was removed in vacuo and the aqueous phase was extracted with EtOAc. After drying over Na₂SO₄, the solvent was evaporated under reduced pressure to give a crude residue which was purified by filtration on silica gel.

(Amorphous solid); ¹H NMR (CDCl₃) δ 1.3 (t, 3H); 2.42 (s, 6H); 2.55 (m, 2H), 2.83 (m, 4H), 7.06 (dd, 1H), 7.19 (d, 1H), 7.45 (m, 1H), 7.88 (br s, 1H)
EIMS: m/z 250 (M⁺); 192, 177, 58 (100)

The compounds according to the present invention are ligands of the 5-HT₆ and/or 5-HT₇ serotonineric receptors; therefore they are useful as medicaments, in particular for the treatment of nervous system pathologies associated with serotonin level deficit, systemic pathologies involving the cardiocirculatory system (hypertension), the gastrointestinal tract (irritable bowel disease).

Amongst the pathologies treated with the compounds of the present invention are: migraine, depression, hypertension, psychosis and other processes involved with functional alterations, brought about by the desynchronisation and/or loss of circadian rhythms (wake/sleep cycle, melatonin synthesis).

Regarding one of the preferred groups of the Formula (I) compounds, in which R₃ is methyl and R₄ is bromo or chloro, and in particular when R₄ is bromo, the molecule gains affinity for the 5-HT₇ receptor subtype. By virtue of this property, use of the compound named ST 1938 is indicated for the treatment of depression, migraine and hypertension, in particu-

lar, to facilitate and improve learning processes of the individuals, and to counteract the desynchronisation of human biological rhythms which bring about mental fatigue, depression and sleep disorders.

Inhibition of binding to 5-HT₆ receptors was determined according to a published method (Monsma, F.J. et al., *Molecular Pharm.*, 1993, 43:320-327). The binding assay has been performed employing rat 5-HT₆ stably transfected to HEK293 (human embryonic kidney cells) with [³H]-LSD (lysergic acid diethylamide) as radioligand. Previously, each compound was dissolved in DMSO to prepare 10 mM stock solution, and then dissolved in H₂O to a final concentration of 0.1 mM. After serial dilutions, eight different concentrations (from 10 μM to 0.001 nM) in duplicate were employed to obtain a competition curve by which to evaluate binding affinity for 5-HT₆ receptor of each test compound. Experimental conditions provided for: 2 nM [³H]-LSD, 100 μM serotonin creatinine sulfate to define non-specific binding and 60 minutes, at 37° C, for incubation of each sample. Following incubation, the membranes were rapidly filtered under vacuum through glass fiber filters (GF/B, Packard). Bound radioactivity was measured with a scintillation counter (Topcount, Packard) using a liquid scintillation cocktail (Microscint 0, Packard). The IC₅₀ of each compound were determined by non-linear regression analysis of the competition curves using Hill equation curve fitting. Then, these values were employed to calculate inhibition constant (K_i) values by which each test compound affinity for 5-HT₆ receptor was expressed. The K_i value was defined by the Cheng Prusoff equation: $K_i = IC_{50} / (1 + ([L] / K_d))$ in which IC₅₀ value is that concentration (nM) of test compounds by which 50% of specific radioligand is displaced from receptor, [L] is the concentration of the specific radioligand in assay and the K_d is the affinity of radioligand for the receptor.

Displacement experiments were carried out in order to determine the affinity of the substance to the 5-HT₇ receptor, according to published

method (Shen, Y. et al.. (1993) *Journal Biological Chemistry* 268: 18220-18204). For the performance of the test, human 5-HT₇ receptor stably transfected to CHO cells (human ovarian cells) were employed and [³H]-LSD (4 nM) as radioligand. Further experimental conditions provided for 10 μ M serotonin as non-specific ligand and 120' at 22° C for incubation of each sample. The respective test compounds were investigated at 8 different concentrations (from 10⁻⁵ M to 10⁻¹² M) in duplicate, to obtain full competition curve. Each compound was previously dissolved in DMSO to obtain a 10⁻³ M stock solution, and then dissolved in H₂O to final concentration of 10⁻⁵ M. The binding reaction of each test compound was interrupted by a rapid filtration under vacuum through glass fiber filters (GF/B, Packard). The filters were then washed several times with an ice-cold buffer. Bound radioactivity was measured with a scintillation counter (Topcount, Packard) using a liquid scintillation cocktail (Microscint 0, Packard). As described above, IC₅₀ values were determined by non-linear regression analysis of each competition curve and K_i values were calculated from the Chen Prusoff equation ($K_i = IC_{50} / (1 + L/K_d)$).

In table 1, 5-HT₆ and 5-HT₇ binding affinity values of each test compound are reported.

Table 1

Affinity for 5-HT₆ e 5-HT₇

Compounds	5-HT ₆		5-HT ₇	
	IC ₅₀ (nM)	K _i (nM)	IC ₅₀ (nM)	K _i (nM)
ST 1936	62	31	527	168
ST 1938	62	32	158	47
ST 2253	52	26	>1000 nM	>1000 nM
Serotonin	171	87	0.64	0.19

ST 1936, ST 1938, ST 2253 display high affinity for rat recombinant 5-HT₆ receptor. In addition, their binding affinity is also greater than that observed for Serotonin.

Among these compounds, the one named ST 1938 also displays highest affinity for human recombinant 5-HT₇ receptor, whereas ST 1936 and ST 2253 show respectively moderate and negligible affinity.

Selected compounds were examined to determine their specificity of binding to 5-HT₆ receptor. Previously, binding affinity for other serotonin sites was evaluated.

In table 2, the affinity values (K_i, nM) of selected compounds to several serotonin subtypes are represented.

Table 2

	Affinity (K _i , nM)			Reference Compounds	
	ST 1936	ST 1938	ST 2253		
5-HT ₆	31	32	26	serotonin	171
5-HT ₇	168	47	>1μM	serotonin	0,19
5-HT _{1a}	>1μM	947	1μM	8-OH-DPAT	3
5-HT _{1b}	>1μM	>1μM	>1μM	serotonin	15,4
5-HT _{1d}	>1μM	>1μM	>1μM	serotonin	1,41
5-HT _{2a}	>1μM	>1μM	>1μM	Ketanserin	0,93
5-HT _{2b}	>1μM	154	84	serotonin	16
5-HT _{2c}	>1μM	>1μM	>1μM	mesulergine	0,56
5-HT ₃	>1μM	>1μM	>1μM	MDL72222	10,3
5-HT ₄	>1μM	>1μM	>1μM	serotonin	57,5
5-HT _{5a}	>1μM	>1μM	>1μM	serotonin	156
5-HT transporter	>1μM	>1μM	>1μM	zimetidine	9,28

It is shown that the compounds ST 1936 and ST 2253 are able to bind, selectively, 5-HT₆ receptors. Furthermore, 5-HT₆ receptor binding specificity of ST 1936 and ST 2253 was examined after evaluating binding affinity to some receptors related to other neurotransmitters.

ST 1936 and ST 2253 were examined at 23 sites. At most of these receptors the selected compounds displayed negligible affinity. In particular, affinity values of ST 1936 and ST 2253 appeared similar or greater than 1000 nM for the following receptors: alpha_{1a} and beta₁ adrenergic; D₁, D₂, D₃, D_{4,4}, D₅ dopaminergic; NMDA, muscarinic (non-selective); N neuronal (α-BGTX-sens.), N neuronal (α-BGTX-ins.) nicotinic, H₁ histaminergic, opiate (non-selective), V_{1a}, V_{1b}, V₂ of vasopressin, ML₁ and ML₂ of melatonin, NA transporter, DA transporter. Further the compounds displayed moderate affinity for alpha_{1b} adrenergic receptor 53 nM and 69 nM respectively for ST 1936 and ST 2253. However, interaction capability for alpha_{1b} receptors of selected compounds were about 2 fold and 3 fold lower than that was evaluated for 5-HT₆ receptor. Whole data demonstrate that the compounds ST 1936 and ST 2253 have a selective affinity for 5-HT₆ receptor.

Relatively to selected compound named ST 1938 which appeared with mixed activity for 5-HT₆ and 5-HT₇ serotonin receptors, it displayed negligible affinity (K_i > 1000 nM) for these sites: H₁; NMDA; PCP; muscarinic receptors; nicotinic receptors, opiate; vasopressin V₁ and V₂; D₁, D₂, D₃, D_{4,4} D₅; DA transporter, NA transporter.

A further object of the present invention relates to pharmaceutical compositions comprising, as active ingredient, at least one Formula (I) compound, singularly or in association with one or more other Formula (I) compounds, or said Formula (I) compound/s in association with other active ingredients used in the treatments of the pathologies described herein, for example other products with activities for the 5-HT₆ and/or

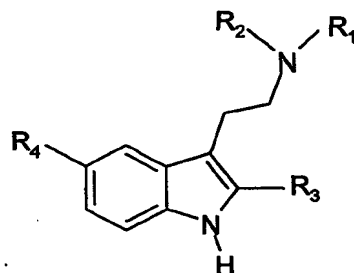
5-HT₇ serotonergic receptors, either as separate dosages or in forms adapted for combined therapy. The active ingredient according to the present invention will be mixed with the appropriate vehicles and/or excipients commonly used in pharmaceutical techniques, as for example, these described in *Remington's Pharmaceutical Sciences Handbook*, latest edition. The compositions according to the present invention will contain a therapeutically effective amount of the active ingredient. The dosage will be determined by those skilled in the art, for example the clinic or the doctor according to the type of pathology being treated and the conditions of the patients, or in accordance with the administration of other active ingredients.

Examples of pharmaceutical compositions are those which allow oral, parenteral, intravenous, intramuscular, subcutaneous, transdermal administration.

Pharmaceutical compositions suited to this purpose are pills, rigid or soft capsules, powders, solutions, suspensions, syrups, solid forms for extemporary liquid composition. Compositions for parenteral administration are, for example, all the injectable forms, whether intramuscular, intravenous, subcutaneous, in the form of solutions, suspensions and emulsions. Liposomal formulations are also mentioned. Controlled release forms of the active ingredient are also included, both for oral administration, such as these coated with the appropriate coating materials, microencapsulated powders, cyclodextrin complexes, and depot forms such as for subcutaneous use or for use as implants.

CLAIMS

1. Use of Formula (I) compounds



(I)

wherein:

R₁ and R₂, the same or different, are H or C₁-C₆ linear or branched alkyl;

R₃ = C₁-C₆ linear or branched alkyl;

R₄ = halogen;

and of the pharmaceutically acceptable salts thereof for the preparation of medicaments, useful as ligands of the 5-HT₆ and/or 5-HT₇ serotonergic receptor.

2. The use according to claim 1, wherein said medicaments are used in the treatment of nervous system pathologies associated to serotonin level deficit, systemic pathologies involving the cardiovascular system, and the gastrointestinal tract.

3. The use, according to claim 2, wherein said medicaments are useful in the treatment of hypertension.

4. The use according to claim 2, wherein said medicaments are useful in the treatment of irritable bowel disease.

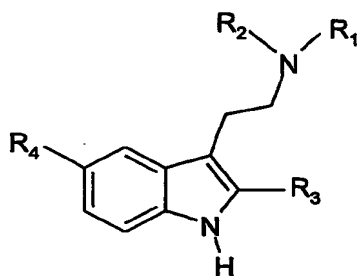
5. The use according to claim 1, wherein said medicaments are useful in the treatment of migraine, depression, hypertension, psychosis and symptoms arising from the desynchronisation and or loss of circadian rhythms (wake/sleep cycles and melatonin synthesis).
6. The use according to claim 1, wherein said medicaments are ligands of the 5-HT₆ serotonergic receptor and are useful in the treatment of depression, mood disorders, psychosis, schizophrenia, motor disorders, cognitive disorders, Parkinson's disease, Alzheimer's disease, Huntington's disease.
7. The use according to claim 1, wherein in the compounds of Formula (I) R₁ is equal to R₂.
8. The use according to claims 1 or 4, wherein in the Formula (I) compound, R₃ is methyl and R₄ is bromo or chloro.
9. The use according to claims 1 or 5, wherein in the Formula (I) compounds (I) R₄ is bromo.
10. The use according to claim 9, wherein the Formula (I) compound is 5-bromo-2-methyl-*N,N*-dimethyltryptamine.
11. The use according to claims 1 or 6, wherein in the Formula (I) compounds (I) R₄ is chloro.
12. The use according to claim 11, wherein the Formula (I) compound is 5-chloro-2-methyl-*N,N*-dimethyltryptamine or 5-chloro-2-ethyl-*N,N*-dimethyltryptamine.
13. The use according to claim 9, wherein said medicaments are useful as ligands of the 5-HT₇ serotonergic receptor.

14. The use according to claim 11 or 12, wherein said medicaments are useful as ligands of the 5-HT₆ serotonergic receptor.

15. The use according to claim 13 for the preparation of medicaments useful in the treatment of depression, migraine and hypertension, in particular to assist or improve the individual learning processes and to counteract the desynchronisation of human biological rhythms giving rise to mental fatigue, depression and sleep disorders.

16. The use according to claim 14 for the preparation of medicaments useful in the treatment of depression, mood disorders, psychosis, schizophrenia, motor disorders, cognitive disorders, Parkinson's disease, Alzheimer's disease, Huntington's disease.

17. Formula (I) compounds



(I)

wherein:

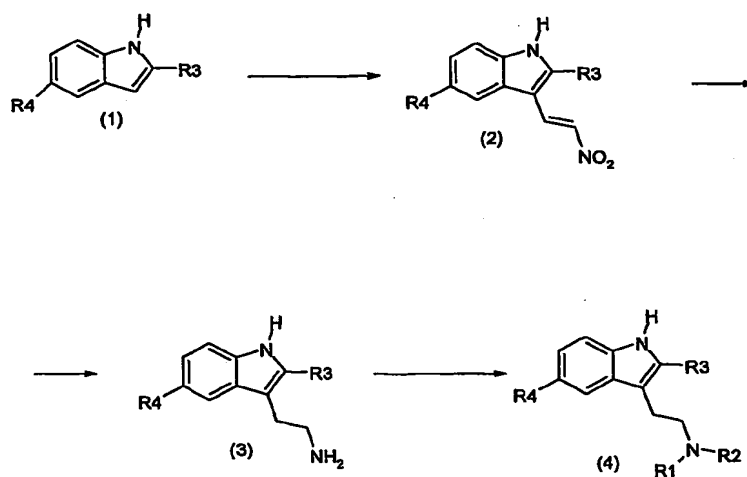
R₁ and R₂, the same or different, are H or C₁-C₆ alkyl;

R₃ = C₁-C₆ alkyl;

R₄ = halogen,

and pharmaceutically acceptable salts thereof, with the proviso that when R₄ is fluoro, chloro or bromo, R₃ is methyl, R₁ and R₂, either the same or different, are not H or methyl.

18. Process for the preparation of the compounds according to claim 17, according to the following scheme:



19. The use of the compounds according to claim 17 as medicaments.

20. Pharmaceutical compositions comprising at least one compound of claim 17 as the active ingredient, admixed with pharmaceutically acceptable vehicles and/or excipients.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/IT 02/00398

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 7 A61K31/405 C07D209/16 A61P1/00 A61P9/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K C07D A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00 34242 A (GLENNON RICHARD A ;ROTH BRYAN L (US); UNIV VIRGINIA COMMONWEALTH () 15 June 2000 (2000-06-15) page 6, line 4 -page 7	1-20
X	LEE M ET AL: "5-TH6 SEROTONIN RECEPTOR BINDING AFFINITIES OF N1-BENZENESULFONYL AND RELATED TRYPTAMINES" MEDICINAL CHEMISTRY RESEARCH, BIRKHAUSER, BOSTON, US, vol. 4, no. 10, 2000, pages 230-242, XP001079522 ISSN: 1054-2523 table 2	1-20
A	WO 00 63203 A (ALLELIX BIOPHARMA) 26 October 2000 (2000-10-26) page 1 -page 2, line 17	1-20
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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G document member of the same patent family

Date of the actual completion of the international search

10 September 2002

Date of mailing of the international search report

25/09/2002

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INTERNATIONAL SEARCH REPORT

International Application No.

PCT/IT 02/00398

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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A	EP 0 937 715 A (MEIJI SEIKA KAISHA) 25 August 1999 (1999-08-25) page 4, line 1 -page 4, line 24 page 37, line 15 -page 37, line 30 -----	1-20
A	N.B. CHAPMAN; K. CLARKE; H. HUGHES: "Synthesis of some 5-substituted-2-methyltryptamines and their N-mono- and N,N-dialkyl derivatives" J. CHEM. SOC, February 1965 (1965-02), pages 1424-1428, XP001099092 page 1427; table 3 -----	17

INTERNATIONAL SEARCH REPORT

Information on patent family members

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WO 0112629	A	22-02-2001	AU 6310300 A EP 1204662 A1 WO 0112629 A1	13-03-2001 15-05-2002 22-02-2001
EP 0937715	A	25-08-1999	EP 0937715 A1 NO 986141 A US 6355642 B1 CA 2259218 A1 WO 9800400 A1	25-08-1999 17-02-1999 12-03-2002 08-01-1998 08-01-1998